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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,354	12/30/2003	Richard L. Moss	054030-0045	7816

31096 7590 01/10/2006

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,354	MOSS ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/25/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 are pending.

Election/Restrictions

Applicant's election with traverse of the invention of group I, claims 1-8 and 14, in the reply filed on November 29, 2005 is acknowledged. The traversal is on the ground(s) that if the search and examination of all the claims of an application can be made without serious burden the examiner must examine them on the merits, even though they include claims to independent or distinct inventions. Applicant argues that a search of the art in the field of the claims of group I will include a search of the art in the field of group II and each is coextensive with the other. Applicant further argues that claim 14, elected group I, recites the production of a transgenic mouse by introducing a nucleic acid molecule according to claim 9. Thus, search of subject matter of claim 14, must, ex facie, include a search of the subject matter of claim 9. Therefore, the Office cannot perform a search of claim 14, group I without completing a search of the subject matter of group II. This is not found persuasive because restriction requirements are set forth for reasons of patentability distinction between each independent invention so as to warrant separate search and search burden. The examiner maintains that groups I and II are distinct because group I is drawn to a transgenic mouse which has distinct and different structure, function and utilities compared to a recombinant nucleic acid molecule of group II. For example, a transgenic mouse can be used as a disease model and a recombinant construct for transforming a cell in vitro. The requirement is still deemed proper and is therefore made FINAL.

Claims 9-13 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 29, 2005.

Claim Objections

Claim 14 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent reference to two sets of claims to different features See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5 and 14 embrace a transgenic mouse characterized by a reduced heart rate having incorporated into its genome a transgene comprising a nucleic acid, which encodes a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase) and interactive micro-domain of cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of said mouse cardiac alpha myosin heavy chain wherein said mouse cardiac alpha myosin heavy chain exhibits: (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) resulting in the transgenic mouse exhibiting a reduced heart rate. Dependent claims of claim 1 limit the modification to an S342G mutation in loop 1 wherein modification comprises a substitution of loop 1 of mouse cardiac alpha myosin heavy chain by a rat or pig or human beta myosin heavy chain loop 1 wherein said modification comprises a substitution of mouse

cardiac alpha myosin heavy chain micro-domain by a non-mouse myosin heavy chain interactive micro-domain.

Claims 6-8 encompass a method of studying molecular and cellular aspects associated with a transgenic mouse having a reduced heart rate or a method for identifying compounds useful for treating or preventing cardiac disease of said transgenic mouse or a method for evaluating the effects of external factors selected from the group consisting of diet, exercise and combinations thereof on cardiac disease of said transgenic mouse.

In determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether a skilled artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are; the breadth of the claims, the nature of the invention, the state of the art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

These factors are analyzed, in turn, and demonstrate that one of ordinary skill in the art will need to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

As a first issue, the claims embrace a transgenic mouse overexpressing a transgene comprising a nucleic acid, which encodes a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain thereby reducing an ADP dissociation rate of mouse cardiac alpha myosin heavy chain. The specification in example I describes that the kinetic properties of myosins encoded by the same MHC isoform gene but derived from different species (e.g. pig, or human β versus rat β), can exhibit greater functional differences than those between distinct phenotypes (α versus β) originating from the same species) (specification p 14). The specification also states that this is an important result because myosins encoded by orthologous genes exhibit much greater sequence homology than myosins encoded by different genes (α versus β), implying that the functional diversity between myosin motor proteins need not be related to overall levels of sequence homology (specification p 14). The specification teaches kinetic differences between rat α and mouse α myosins in vitro (example I). Example II describes the cloning of the mouse αMHC gene and the construction of a rat αMHC/pig β loop knock-in targeting vector for subsequent transgenic animal production (specification p 53). In addition, the specification describes that a transgenic mouse is the model of choice because mice provide genetic and protein backgrounds that are generally representative of mammalian systems, including humans (spec p 13, lines 9-14). The specification contemplated that a transgenic mouse with an ortholog transgene is predicted to have slower speed, greater power and reduced heart rate better resembling larger mammals (specification p 16, lines 9-11). However, the specification has failed to provide guidance

and/or working examples correlating to the creation of such a transgenic mouse expressing a mouse cardiac alpha myosin heavy chain including such a modification (an ortholog gene) which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain molecule wherein said mouse cardiac alpha myosin heavy chain exhibits: (a) reduced contractility (speed of contraction); and (b) increased power generating capability (work capacity) and exhibiting a reduced heart rate. One of skill in the art could not rely on the transgenic art to make such a transgenic mouse phenotype because neither the art nor the specification teach said transgenic mouse. The state of the transgenic art has set forth that phenotypes resulting from expression of a transgene are unpredictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms, which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappell et al, Current Opinion in Biotechnology 3:548-553, 1992) (p 549, col. 2, 2nd paragraph). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, J. Biotechnology, 34: 269-287, 1994) (p 281). "The position effect" and unidentified control elements also are recognized to cause aberrant transgene expression (Wall (1996) Theriogenology 45, 61, 2nd paragraph, line 9 to page 62, line 3). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, Molecular Biotechnology, 7: 253-265, 1997) (p 256, col. 1 -2, bridge paragraph). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, page 256,

lines 3-9). These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron, page 256, lines 10-13). Sigmund (2000) states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, 1st paragraph, lines 1-7). Given the lack of guidance and relevant teachings provided by the specification with respect to the unpredictable nature of phenotypes resulting from a transgenic mouse whose genome comprises a nucleic acid sequence encoding a mouse cardiac alpha myosin heavy chain including a modification which reduces electrostatic interaction between loop 1 (ATPase loop) and interactive micro-domain of cardiac alpha myosin heavy chain, it would have required undue experimentation for the skilled artisan to make and use the transgenic mouse embraced by the claims.

As a second issue, the following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to claim 14 as it relates use of embryonal cells to make a transgenic mouse and germline transmission of embryonal cells.

Both the specification and the state of the art have taught that transgenic knock out technology requires the use of embryonic stem cells or fertilized oocytes that have been genetically manipulated to comprise a disruption/mofification in a nucleotide sequence of interest. The claims however require an embryonal cell which is broader than an ES cell or fertilized oocyte. However, the specification has not provided guidance or working examples correlating to use of embryonal cells to make a transgenic mouse and germline tansmission of other embryonal cells.

With regard to the claim breadth directed to use of embryonal cells [see step (a) of claim 14], the specification has failed to provide guidance correlating to germiline transmission of

embryonal cells other than ES cells or fertilized oocytes, embryonal cells and germline transmission. The specification described that "According to the present invention, a transgenic mouse is a mouse that includes a recombinant nucleic acid molecule (e.g. transgene) that has been introduced into the genome of the mouse at the embryonic stage of the mouse's development as such, that the transgene will be present in all of the germ cells and somatic cells of the mouse" (spec p 6, lines 1-4). However, it is unpredictable if other embryonal cells would contribute to the germline. For example, it is well known in the knockout art that embryonic stem (ES) cells achieve germline transmission of a disrupted target gene. See Hochepied et al (Stem Cells, 2004, 22: 441-447) in the abstract, which reports "Transmission of the genotype to the offspring of chimeras has only been achieved with *M. musculus* ES cells, limiting targeted mutagenesis using ES cells to this species". Although transmission of ES-cell derived genome to the germ cells and further to the offspring has proved impossible in species other than the house mouse *M. musculus*, Hochepied et al has further reported that "even within *M. musculus* species certain genetic backgrounds have been reported to be less permissive or even non-permissive for germline –competent ES cell derivation. See the first paragraph, in the second column of page 444. Schoonjans et al (Stem Cells, 2003, 21: 90-97) supports the findings of Hochepied by observing that efficiency of derivation of germline-competent ES cell lines from inbred mouse strains, with specific genetic backgrounds, is greatly strain dependent. See page 90 of Schoonjans, in the introduction. Also it is well known that creation of a transgenic mouse by pronuclear injection into a fertilized oocyte will contribute a transgene to the germline. Neither the specification nor the state of the art has provided guidance relating to production of a transgenic mouse through the use of other embryonal cells. Accordingly, with regard to claim 14 the specification has failed to provide guidance correlating to the use of other embryonal cells and germline transmission of a modified gene. The claims as such are not

enabled for germline transmission of other embryonal cells. Given, the lack of guidance and relevant teachings provided by the specification with respect to use of other embryonal cells, it would have required undue experimentation for the skilled artisan to make and use the transgenic mouse embraced by the claims.

As a third issue, claims 6-8 are directed to methods of studying molecular and cellular aspects associated with a transgenic mouse having a reduced heart rate, identifying compounds useful for treating and preventing cardiac disease of a transgenic mouse or a method for evaluating the effects of external factors selected from the group consisting of diet, exercise and combinations thereof on cardiac disease of a transgenic mouse. The specification contemplated the transgenic mammals of the invention provide methods to study the molecular and cellular aspects of heart muscle disease and heart failure diseases (specification, p 9). For instance, a transgenic animal of the present invention may be sacrificed, and the cells and/or tissues examined at the cellular or molecular level and compared to cells and/or tissues from transgene-negative littermates. In addition, the specification contemplates the transgenic animals of the invention may be used to study the effects of overexpression of mutant alpha myosin heavy chain (MHC). For example, the effects of overexpression of alpha MHC on heart morphology and function, myocyte morphology and function, the expression of other molecules, the development and treatment of heart muscle disease and heart failure, can be evaluated. Furthermore, the specification contemplates the transgenic animals of the invention provide methods to test drugs candidates for prevention or treatment of heart muscle disease and heart failure. In addition, instant invention claimed transgenic mammals to study the effects of external factors on heart muscle disease and heart failure such as diet and exercise (specification p 11). However, neither the specification nor the art of record provide guidance and /or working examples for the claimed methods. The specification has failed to provide

specific guidance and/or working examples of what types of specific molecular and cellular aspects are associated with claimed transgenic mouse. The specification failed to provide a transgenic mouse with a reduced heart rate phenotype which phenotype is correlated to a specific heart disease in order to study molecular and cellular aspects associated with heart diseases or to identify any compounds for either treatment or prevention of a cardiac disease or evaluating the effects of diet or exercise and combinations thereof on any cardiac disease. Given the lack of guidance and/or working examples by the specification correlating a transgenic mouse with reduced heart rate phenotype and cardiac disease treatment or drug efficacy on any cardiac disease it would have required undue experimentation to practice the invention as claimed for treating cardiac diseases by overexpression of mutant alpha MHC gene without a reasonable expectation of success.

As a final issue, claims 1-5 and 14 embrace a homozygous or heterozygous transgenic mouse with a reduced heart rate. However, the specification has not provided working examples correlating homozygous transgenic mouse with reduced heart rate phenotype to heterozygous transgenic mouse. It is well known in the art that heterozygous mice because they carry one copy of the wild type allele do not always exhibit phenotype similar to knock out mice.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the treatment of a disease, particularly cardiac diseases, the lack of direction or guidance provided by the specification for treatment of a cardiac disease, the absence of working examples that correlate to the treatment of a cardiac disease, the unpredictable state of the art with respect to if other embryonal cells would contribute to the germline, and the breadth of the claims directed to all cardiac diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 recites the limitation "transplanting the transgenic embryonal target cell" in claim 14 subset (b) first line. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

No claim is allowed. The claims appear to be free of the prior art of record but are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla, can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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